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09/933,548	08/20/2001	Christopher William Ogden	NORT 100	6550

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PATREA L. PABST
HOLLAND & KNIGHT LLP
SUITE 2000, ONE ATLANTIC CENTER
1201 WEST PEACHTREE STREET, N.E.
ATLANTA, GA 30309-3400

EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,548	OGDEN ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,23-34, 36, 37, and 39-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,15,16 and 39-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The following restriction requirement is made below in view of the statements set forth in the Petition Decision

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I, claims 1-4, 5-9, and 15-16 are drawn to a method of determining susceptibility, diagnosing prostate cancer and predicting patient outcome through nucleic acid analysis classified in for example Class 435, subclass 6, 91.2 and Class 536 subclasses 23.1 and 24.1.

Group II, claims 1-4, 10, 11, and 13-16 are drawn to a method of determining susceptibility, diagnosing prostate cancer and predicting patient outcome through protein analysis classified in for example Class 435, subclass 7.1.

Group III, claims 1-4, 10-13, 15-16 are drawn to a method of determining susceptibility, diagnosing prostate cancer and predicting patient outcome through antibody analysis classified in for example Class 435, subclass 7.1.

Group IV, claims 17, 18, 21, and 22 are drawn to a method of using a specific agent to determine the level of a nucleic acid classified in Class 435 subclass 6 and Class 514 subclass 44.

Group V, claims 17, 19, and 20-22 are drawn to a method of using a specific agent to determine the level of a protein classified in for example Class 435, subclass 7.1 and Class 514 subclass 44.

Group VI, claim 23, 30-35, and 36 are drawn to a kit for detecting nucleic acids and to a nucleic acid encoding, genetic construct , and a nucleic acid based pharmaceutical composition classified in for example Class 435, subclass 6 and 514 subclass 44.

Group VII, claim 23 is drawn to a kit for detecting proteins classified in for example. Class 514, subclass 2

Group VIII, claims 24-29 and 37 are drawn to a method of treating prostate cancer through nucleic acid administration classified in for example, Class 514, subclass 44.

The inventions are distinct, each from the other because of the following reasons:

a. Inventions I and II, I and III, I and IV, I and V, I and VIII, II and III, II and IV, II and V, II and VIII, III and IV, III and V, III and VIII, and IV and V and IV and VIII are drawn to patentably distinct methods that involve different method steps, include different reagents and have different objectives. Invention I involves determining susceptibility through nucleic acid analysis. The invention of Group II involves determining susceptibility, diagnosing prostate cancer and predicting patient outcome through protein analysis. The invention of Group III is drawn to a method of determining susceptibility, diagnosing prostate cancer and predicting patient outcome through antibody analysis. Group IV is drawn to a method of using a specific agent to determine the level of a nucleic acid. Group V is drawn to a method of a method of using a specific agent to determine the level of a protein. Finally Group VIII is drawn to a method of treating prostate cancer through nucleic acid administration. Therefore the methods are distinct over one another.

b. Inventions VI and VII are patentably distinct in structure and physiochemical properties. Invention VI is drawn to nucleic acids whereas invention VII is drawn to proteins. Because nucleic acids are composed of nucleotides and proteins are composed of amino acids, the inventions have different structural and functional properties. Furthermore, the compositions are utilized in different methodologies, such that nucleic acids may be utilized in hybridization

assays, while the proteins may be utilized in ligand binding assays or to generate antibodies. The proteins of invention VII do not require the particular products of the nucleic acids of group VI since the proteins of invention VII can be isolated from natural sources or chemically synthesized.

Applicant is advised that examination will be restricted to only the elected biomolecule (DNA, Protein or Ab): and the election of such should not be construed as a species election. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claims 1-4, 10, 11, 13, 15, 16, 17, 21, 22, and 23. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01. FOR EXAMPLE…If applicant elects group I, they will be prosecuting the group's linking claims to the extant that they disclose nucleic acids. Additionally, if applicant elects group VII, they will further be prosecuting the claim 23 linking claim to the extant that it reads only on the kit comprising an agent capable of detecting a protein etc.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions I-VIII require different searches that are not coextensive, examination of these claims would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

This restriction requirement has been herein provided to clarify the prosecution record. Since applicant has previously elected group I drawn to a method of nucleic acid analysis, and the invention has been searched and examined no further election is possible at this time, as the inclusion of this restriction requirement was meant solely to clarify the prosecution record in light of the decision on applicant's petition.

FINAL REJECTION

This action is written in response to applicant's correspondence submitted 10/31/2003 and in light of the decision on the petition submitted by applicants on October 1, 2003. Claims 2 and 3 have been amended, claims 21, 22, and 38 were previously canceled, and claims 39-49 have been added. Claims 1-20, 23-34, 36, 37, and 39-49 are pending. Claims 1-9, 15-16 and new claims 39-49 are presently examined. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-9, 15-16, and new claims 39-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-9 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing prostate cancer in a human patient comprising the steps of (i) obtaining a sample of the tissue, containing mRNA, in which prostate cancer is suspected or in which prostate cancer may be or has been found and (ii) detecting the presence or absence of mRNA expression which is associated with prostate cancer, does not reasonably provide enablement for (i), a method of determining the susceptibility of a human patient to prostate cancer or predicting the relative prospects of a particular outcome of prostate cancer predisposition by obtaining a sample containing only cells from tissues or a sample of urine, semen, blood, or lymphatic circulation, and (ii) determining whether the sample contains any level of any nucleic acid of Pax 2 associated with prostate cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-9 and 15-16 are broadly drawn to a method of determining the susceptibility of a human patient to prostate cancer or predicting the relative prospects of a particular outcome of prostate cancer predisposition by obtaining a sample containing only cells from tissues or a sample of urine, semen, blood, or lymphatic circulation, and (ii) determining whether the sample contains any level of any nucleic acid of Pax 2 associated with prostate cancer. The specification teaches a method of detecting the expression, presence alone, of Pax2 mRNA in all three established prostate cancer cell lines(LNCaP, DU-145, and PC-3), in 3 out of 5 channel prostate cancer TURP tumor samples, and in 10 out of the 15 radical prostatectomy specimens from patients with prostate cancer all following RNA extractions, RT-PCR and Southern hybridizations. The specification also teaches the inability to detect Pax 2 mRNA expression in benign prostatic hyperplasia(BPH) samples in all five samples tested. The specification then teaches that Pax 2 expression is linked with prostatic cancer but not with benign prostatic hyperplasia. The specification has not established a clear correlation between the susceptibility of a human patient to prostate cancer or predicting the relative prospects of a particular outcome of prostate cancer predisposition by obtaining a sample containing only cells from tissues or a sample of urine, semen, blood, or lymphatic circulation, and (ii) determining whether the sample contains any level of any nucleic acid of Pax 2 associated with prostate cancer G/G genotype and the occurrence of bipolar II depressive disorder. More specifically, the specification does not teach the detection of Pax 2 mRNA expression in a patient without cancer, solely as a means to determine how susceptible a patient is to prostate cancer. The specification omits any teaching concerning the detection of Pax 2 mRNA as a predisposing factor to the patient's future development of prostate cancer. The specification itself on Page 27 asserts that "Pax 2

expression may be detected in prostate cancer tissue, particularly from invasive prostate cancer, but may not be detected in normal prostate tissue". Furthermore, the specification omits any teaching of the detection method's ability to determine particular outcomes of prostate cancer. On page 62, five prostate samples were obtained from patients known to have metastatic prostate cancer, but the results of this study were the same as those done with non-metastatic prostate samples thereby not teaching any difference in one particular outcome at least being metastaic potential, for example, through the detection of Pax 2 mRNA. Furthermore, the specification teaches only the detection of mRNA expression, presence or absence, through RT-PCR followed by gel electrophoresis and Southern blot detection methods. The specification has not taught a variant grade or level at which the Pax 2 mRNA is detected only that it "is" or "is not". The specification has not taught that Pax 2 DNA or any other Pax 2 nucleic acid besides Pax 2 mRNA is present in prostate cancer cell lines and tissue samples. The specification has further omitted teachings of Pax 2 mRNA being found in any cell from a prostate tissue or in urine, semen, blood, or lymphatic circulation, only in tissue samples from the prostate and from well known prostate cell lines. The specification does not teach a method broadly drawn to determining the susceptibility of a human patient to prostate cancer or predicting the relative prospects of a particular outcome of prostate cancer predisposition by obtaining a sample containing only cells from tissues or a sample of urine, semen, blood, or lymphatic circulation, and (ii) determining whether the sample contains any level of any nucleic acid of Pax 2 associated with prostate.

As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The

amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one cannot readily anticipate a method broadly drawn to determining the susceptibility of a human patient to prostate cancer or predicting the relative prospects of a particular outcome of prostate cancer predisposition by obtaining a sample containing only cells from tissues or a sample of urine, semen, blood, or lymphatic circulation, and (ii) determining whether the sample contains any level of any nucleic acid of Pax 2 associated with prostate. One cannot anticipate whether or not a subject will get prostate cancer if the Pax 2 mRNA cannot be detected in the normal prostate(Specification Pg27). Also, it is highly unpredictable to assume that all nucleic acids besides just mRNA can be found in any cell from tissues or in a sample of urine, semen, blood, or lymphatic circulation in addition to the samples from prostate tissue that have been taught in the specification. In the absence of specific guidance as to how to identify both the susceptibility and the ability to predict the outcome of prostate cancer through the detection of all nucleic acids in cells from tissues or a sample of urine, semen, blood, or lymphatic circulation, it would require undue experimentation, if not impossible to detect a Pax 2 DNA in a blood sample that may not even be present in a normal prostate sample. The unpredictability in the art is

emphasized by the teachings in the Applicant's specification regarding the lack of Pax 2 expression in normal prostate tissue with regard to the ability of the method to determine a patient's susceptibility to prostate cancer. The prior art corroborates the unpredictability in the art with respect to the teaching of a method that can predict the relative prospects of a particular outcome of prostate cancer concerning chromosome 10 alterations in Gray et al. It should be noted that the art teaches that there is no clear correlation of loss of chromosome 10q with tumor stage or grade, (Gray et al. Cancer Research 55, 1995) which adds further unpredictability about this inventions ability of predicting outcomes by detection of Pax2(located also on 10q). With respect to the present invention, one cannot readily anticipate the method's ability to determine susceptibility and predict outcomes of prostate cancer thorugh the detection of any nucleic acid in samples other than tissue samples from the prostate. Such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

The specification provides no guidance as to how to predictably identify additional samples wherein the claimed methods will result in the detection of Pax 2 mRNA in a certain level in any sample other than tissue that would be correlated with prostate cancer. Furthermore, the specification fails to teach how these detected nucleic acids actually result in any of the claimed method's ability to predict susceptibility or disease outcomes. Consequently, the resulting levels of Pax 2 will be variable and unpredictable, if not prophetic making the comparison of levels, not even defined in the specification, of nucleic acids require undue experimentation. The ability to establish a correlation between the aforementioned methods and

any level detected from any nucleic acid in a method broadly drawn to determining the susceptibility of a human patient to prostate cancer or predicting the relative prospects of a particular outcome of prostate cancer predisposition by obtaining a sample containing only cells from tissues or a sample of urine, semen, blood, or lymphatic circulation, and (ii) determining whether the sample contains any level of any nucleic acid of Pax 2 associated with prostate is highly unpredictable and can only be determined through extensive, random, trial and error experimentation. Therefore, neither the specification nor the art provides the guidance necessary to practice the method as claimed. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

Response to Arguments:

Applicants traverse this rejection to the extent that it is applied to the claims as amended. Applicants first assert that the Gray reference was improperly cited by the examiner as it "cannot be used to demonstrate the unpredictability of the present invention as it refers to a distinct technical field". While applicants argument is acknowledged, the examiner asserts that the Gray reference was cited to show the unpredictable nature in this region of the genome and the unpredictability involved in attributing tumor stage, grade, or progression to the detection of a single event. On pages 4802-4803, the reference teaches that uncertainty exists concerning the ability to classify or correlate the loss of 10q(or in this present case, the expression of Pax 2 mRNA) with either progression or genesis of prostate carcinogenesis. The reference teaches that upon finding an event(in this case, Pax 2 mRNA expression) in both early and late stage tumors, and not in benign hyperplastic tissue, makes unpredictable the determination of the events

association with a particular stage of prostate carcinogenesis. As such, the examiner maintains the inclusion of this reference as support for the unpredictability involved in practicing the presently claimed method.

Applicants further respectfully submit that the present disclosure enables a person of ordinary skill in the art to use the claimed methods to detect Pax 2 mRNA in prostate tissue, urine, semen, blood, or lymphatic circulation without undue experimentation. While the argument is acknowledged, and the referenced pages of the specification have been reviewed, the argument is not found to be convincing as it is maintained that detecting Pax 2 nucleic acids in any other bodily fluid or specimen is highly unpredictable as the specification teaches only methods in which Pax 2 mRNA is detected in cancerous prostate tissue or cell lines. While applicants suggest, or merely prophesize, that prostate cells could be found in urine, blood, semen, and lymphatic circulation, the unpredictability in how to use this sort of approach in detecting the specific mRNA of Pax 2 is quite large, if even possible. Furthermore, page 13 of the specification teaches the unpredictability involved in this venture as "it will be appreciated that quantification of Pax 2 expression may not be informative, for example in some samples containing more than one cell type"(Lines 5-7). In summary, the rejection under 112 1st paragraph is maintained and further applied to the new claims as the present application is enabled only for a method of diagnosing prostate cancer in a human patient comprising the steps of (i) obtaining a sample of the tissue, containing mRNA, in which prostate cancer is suspected or in which prostate cancer may be or has been found and (ii) detecting the presence or absence of mRNA expression which is associated with prostate cancer.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS

New Matter

Claims 2-9, 15-16, and 39-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "comparing the amount of any Pax 2 mRNA detected in the test sample with the amount of any Pax 2 mRNA detected in a control sample known to contain non-cancerous or non-metastatic cells" in claims 2 and 3, and the limitation of "at least 1.5 fold higher than the amount of detectable Pax 2 mRNA in the sample of non-cancerous or non-metastatic cells" in claims 40 and 42 both appear to represent new matter. The specific basis for these limitations identified in the specification by applicant(Pgs 9 and 10) did not provide basis for these limitations, nor did a review of the specification by the examiner find any basis for the limitations. Since no basis has been identified, the claims are rejected as incorporating new matter.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number until 1/13/2004 is (703) 306-0284 and 1/14/2004 and after will be (571)272-0748. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (703)308-2199. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)308-1119. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

1/6/2004

CARLA J. MYERS
PRIMARY EXAMINER